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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/654,276	09/01/2000	Smadar Cohen	9124.117US01	5848

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/21/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/654,276	Cohen
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 10, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5, 6, 9, 10, and 16-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 5, 6, 9, 10, and 16-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment and response received on 7/10/02 has been entered. Claims 4, 7, 8 and 11-15 have been canceled. New claims 19-21 have been added. Claims 1-3, 5-6, 9-10, and 16-21 are pending in the instant application. An action on the merits follows. Please note that the examiner of record for this application has changed, see page 7.

The text of those sections of Title 35, US code, not included in this action, can be found in the previous office actions.

Claim Rejections - 35 USC § 112

The rejection of original, amended, or new claims 1-3, 5-6, 9-10, and 16-21 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained in part. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that amendment to the claims to recite particular cell types for use in the present invention overcomes the issues raised by the previous examiner regarding the lack of enablement in the specification for repairing damaged myocardium using any type of cell in applicant's disclosed matrix. The applicant has amended the claims to recite fetal cardiomyocytes, neonatal cardiomyocytes, adult cardiac cells, fibroblasts, smooth muscle cells, endothelial cells,

skeletal myoblasts, mesenchymal stem cells and embryonic stem cells. The previous office action noted that the specification provides working examples which enable the use of fetal or neonatal cardiomyoctes or autologous adult myocytes. While endothelial cells are also seeded into the matrix in examples 1 and 2, it is in the context of a co-culture of cardiomyocytes and endothelial cells, not simply endothelial cells by themselves. While the specification provides an enabling disclosure for growing cardiomyocytes **and** endothelial cells or fibroblasts or smooth muscle cells, it is clear from the specification's disclosure that the presence of the cardiomyocyte is essential for achieving the intended therapeutic effect, e.g. the production of cardiac like tissue and the repair of cardiac damage. Furthermore, while embryonic stem cells and mesenchymal stem cells have the genetic **potential** to develop into cardiac myocytes, these progenitor cells also have the capacity to develop into a number of other different non-muscle cells. The specification fails to provide any guidance as to the particular combination of factors and conditions necessary to promote the differentiation and development of embryonic or mesenchymal stem cells into cardiac myocytes or myoblasts. The specification only identifies two growth factors, VEGF and FGF, which have been reported in the prior art to be capable of stimulating angiogenesis. The specification does not identify any growth factor or combination of growth factors capable of promoting the growth and differentiation of any type of stem cell. Further, the specification does not teach which combination of factors, or their necessary concentrations, are capable of causing the differentiation of stem cells into any particular cell type. In the absence of any specific teachings, it

would require undue experimentation to determine the conditions under which embryonic or mesenchymal stem cells can be induced to differentiate into muscle cells *in vitro* or *in vivo.*

The applicant also argues that the amendment of the claims to recite "soluble growth factors" overcomes the previous examiner's concerns regarding the lack of enablement for releasing any and all soluble factors into the graft. As noted above, the specification fails to identify or provide guidance for the use of any growth factors other than VEGF and FGF. While the applicant's amendments have limited the claims to recite "soluble growth factors", the specification fails to teach any growth factors which are not angiogenic growth factors. The applicant is reminded that 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970).

The applicant further argues that the skilled artisan would know how to use immunosuppressive agents to prevent graft rejection and that the specification's disclosure indicates that the use of syngeneic, allogeneic, or xenocompatible tissue. The claims or record place no limitation on the origins of the cells for growth in the matrix and thus read on the use of any type of xenogeneic cells. Further, applicant's example using allogeneic cells used fetal allogeneic cells. The prior art teaches that fetal cells are substantially less immunogenic than their adult counterparts, and that as a result, fetal allografts are less susceptible to graft rejection. For this reason, the scope of enablement was indicated to include fetal cardiomyocytes without any limitation to their origin. However, adult tissue, as discussed in detail in the previous office action,

is subject to substantial allogeneic or xenogeneic immune responses. The specification does not provide any guidance as to measures or methods necessary to prevent destructive allogeneic or xenogeneic immune responses following the transplantation of the matrix containing the allogeneic or xenogeneic tissue. Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997).

Therefore, for reasons of record as discussed in detail above, the specification fails to provide an enabling disclosure for the scope of applicant's invention as claimed.

The rejection of claims 11-15 under 35 U.S.C 112, second paragraph, is withdrawn in view of applicant's cancellation of the claims.

Claim Rejections - 35 USC § 102

The rejection of claims 1-4, 9, and 11-18 under 35 U.S.C. 102(a) over Leor et al. is withdrawn in view of applicant's cancellation of the claims or amendments to the claims to recite

the inclusion of controlled-release microspheres comprising soluble growth factors.

The rejection of claims 11-17 under 35 U.S.C. 102(b) over Shapiro et al. is withdrawn in view of applicant's cancellation of the claims or amendments to the claims to recite the inclusion of controlled-release microspheres comprising soluble growth factors.

Claim Rejections - 35 USC § 103

The rejection of claims 1-4, and 7-8 under 35 U.S.C. 103(a) over Mickle et al. in view of Osiris Therapeutics, Shapiro et al., and Cohen et al. is withdrawn in view of applicant's cancellation or amendment to the claims.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., AU 1632, whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER